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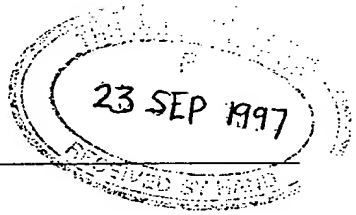

Your reference
PCS9455JRH-PROV

9720228.7

23 SEP 1997

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

PARASITICIDAL FORMULATIONS

2 Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name
PFIZER LIMITED

Country *(and State of incorporation, if appropriate)*
UNITED KINGDOM

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases,** please give the following details:

Address
RAMSGATE ROAD
SANDWICH, KENT

UK postcode CT13 9NJ
(if applicable)

Country UNITED KINGDOM

ADP number
(if known) 6892673001

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant (if any)**

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

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UK postcode
(if applicable)

Country

ADP number
(if known)

3
An address for service in the United Kingdom must be supplied.
Please mark correct box

3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ ***go to 3b***

⬇ ***Please give details below***

Agent's name
J.R. HAYLES
Agent's address
PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT
Postcode CT13 9NJ

Agent's ADP number 6409 593 002

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode
ADP number
(if known)

Daytime telephone number *(if available)*

4 Reference number

4 Agent's or applicant's reference number *(if applicable)* PCS9455JRH-PROV

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

⬇ *please give details below*

❑ number of earlier application or patent number

❑ filing date *(day month year)*

❑ and the Section of the Patents Act 1977 under which you are claiming:

Please mark correct box

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	1	Description	5
Abstract		Drawing(s)	1

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

9 Request

I/We request the grant of a patent on the basis of this application.

Please sign here ➡

Signed James Hayes Date 23/09/1997

(day month year)

A completed fee sheet should preferably accompany the fee.

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

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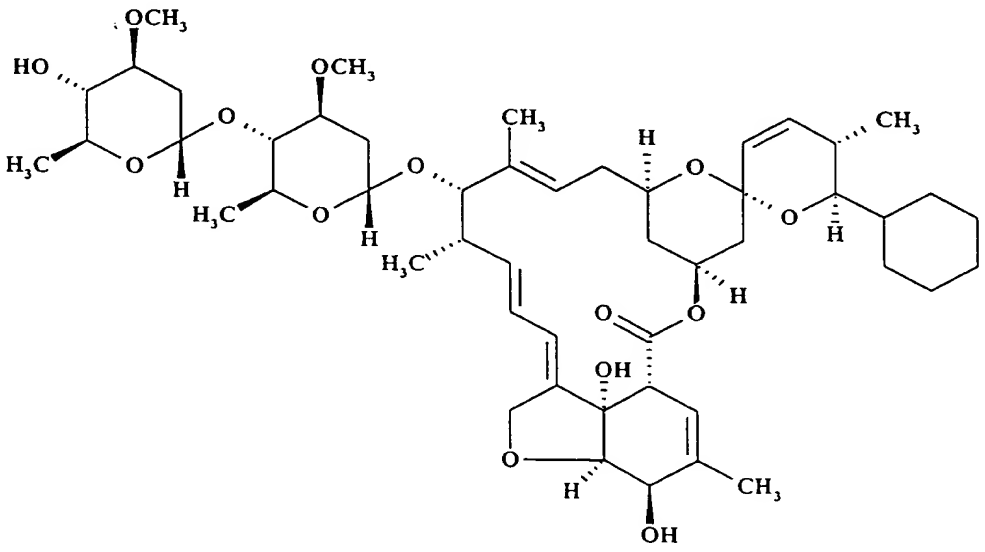
PCS9455JRH-PROV

This invention relates to a simple, solid, subcutaneous implant containing a parasiticidal compound having low aqueous solubility, which is particularly useful for administration to cattle and sheep.

A number of potent macrocyclic parasiticidal compounds are known, including the avermectins and milbemycins. UK Patent N° 1,573,955 discloses a family of avermectin compounds (including avermectins B1a and B1b) which are indicated as parasiticides.

22,23-Dihydroavermectin B1 (ivermectin, disclosed in EP 1689) is available commercially in an injectable formulation (sold as IVOMEC™). Ivermectin is a mixture of at least 80% 22,23-dihydroavermectin B1a (having a 25-sec butyl group) and not more than 20% of 22,23-dihydroavermectin B1b (having a 25-isopropyl group).

25-Cyclohexyl-avermectin B1 (doramectin, disclosed in EP 214731) has the following structure,



and is available commercially in an oil formulation for injection (sold as DECTOMAX™) for the treatment and prevention of internal and external parasite infestations in cattle. The oil formulation is described in European Patent N° 393890.

The milbemycins are similar in structure to the avermectins, except that they are unsubstituted at the 13-position.

Although formulations such as DECTOMAX™ have been successful, there is a need for further formulations which are convenient to administer and which provide prolonged protection against parasites.

Thus, according to the present invention, there is provided a solid subcutaneous implant consisting essentially of: at least one parasiticidal compound having low aqueous solubility; and conventional tabletting excipients including a bulking agent.

"Consisting essentially of" means that at least 95% by weight of the implant is made up of the listed components. Preferably, at least 99% by weight of the implant is made up of the listed components.

Suitable parasiticidal compounds are those having an aqueous solubility below 100 μg/ml, for example the avermectins and milbemycins. Doramectin is of particular interest (which has an aqueous solubility of 0.6 μg/ml at pH 7). Ivermectin is also of interest.

Preferably, the bulking agent is lactose. Other suitable bulking agents include other sugars, microcrystalline cellulose (which is available commercially as AVICEL™) and dicalcium phosphate.

Other conventional tabletting excipients which may be present include magnesium stearate, which acts as a lubricant to facilitate tabletting. Typically, magnesium stearate will make up about 3% of the implant, by weight. Binding agents may also be included in the formulation to aid granulation and compressibility. Examples of binding agents include starch, gelatin and polyvinyl pyrrolidone. Typically, the binding agent, when present, will make up between 2 to 10% of the implant, by weight.

A further tabletting excipient which the implants of the invention may optionally contain is a tablet disintegrant. Suitable tablet disintegrants include sodium starch glycolate, which

is available commercially as EXPLOTAB™. Other disintegrants which may be mentioned are dicalcium phosphate and cross-linked starch. Typically, the disintegrant, when present, will make up about 5% of the implant, by weight.

Preferably, the parasiticidal compound (or compounds) makes up between 10 and 50% of the implant, by weight, more preferably from 20 to 45% of the implant, by weight, for example 40%.

The implants of the invention may be implanted under the skin of various parts of the animal to be treated, for example the flank, the base of the tail or the ear. However, because ears are removed during the meat rendering process, it is preferred that the implants are adapted for implantation into the ears of cattle or sheep.

To facilitate such implantation, the implants are preferably rod-shaped, and can be implanted conveniently using a conventional hand-operated implant gun. Suitably, rod-shaped implants are 5 mm in length and have a circular cross section of 2 to 3 mm diameter.

According to the invention, there is also provided a method for the treatment or prevention of parasitic infections which comprises administering an implant as defined above to an animal in need of such treatment.

Parasitic infections of particular interest are those caused by endoparasites including helminthiasis (most frequently caused by nematode worms in the gastrointestinal tract). The implants are also useful in treatment or prevention of ectoparasite infections such as of ticks, mites, lice, fleas, blowfly, biting insects and migrating dipterous larvae.

The dosage to be administered will depend on the animal to be treated, the parasiticidal compound being used, and the condition to be treated. However, a suitable dose of doramectin is 0.5 mg/kg of animal body weight. Typically, an implant according to the invention will contain about 10 mg of doramectin. Thus, for a typical cow weighing 120 kg, 6 implants will be needed. This provides sustained protection for a season.

The implants of the invention may be prepared by dry- or wet-mass granulation followed by milling and compression into the desired shape using conventional techniques.

The duration of action of the implants of the invention may be determined by measuring blood plasma levels in cattle following implantation. These levels have been correlated with antiparasitic activity of the compounds which have established that for effective control of helminths a blood plasma level of about 2 ng/ml needs to be maintained, and that for effective control of single-host ticks a blood plasma level of about 5 ng/ml needs to be maintained.

The invention further provides a solid subcutaneous implant comprising at least one parasiticidal compound having low aqueous solubility; and conventional tabletting excipients including a bulking agent.

The invention is illustrated by the following examples, and accompanying Figure 1, which shows the blood plasma levels in cattle achieved by the implants prepared in Examples 1 and 2.

Example 1

Doramectin implant

Components	Specification	mg/unit	% by weight
Doramectin[a]	Pfizer	10.000	40
β-anhydrous lactose	Ph Eur	14.250	57
Magnesium stearate	Ph Eur	0.750	3
Total		**25.000**	**100**

[a] mean particle size 19.27 μm (volume mean diameter)

The components, except magnesium stearate, were blended together in a blender for 15 minutes. The blend was then sieved through a 680 μm mesh screen and blended for a

further 15 minutes. After that, half of the magnesium stearate was added and blending continued for 5 minutes, after which the blend was compressed to form "slugs". The slugs were then milled to form granules, and the size fraction 250-355 μm was collected.

The collected granules were then blended for 15 minutes, and then the remaining half of the magnesium stearate was added and blending continued for 5 minutes. The blend was then compressed on a suitable tablet machine using 2 mm tooling to produce rod-shaped implants of 2 mm diameter and 5 mm length.

Example 2

Doramectin implant containing a tablet disintegrant

Components	Specification	mg/unit	% by weight
Doramectin[a]	Pfizer	10.000	40
β-anhydrous lactose	Ph Eur	13.000	52
Sodium starch glycolate (EXPLOTAB™)	BP	1.250	5
Magnesium stearate	Ph Eur	0.750	3
Total		**25.000**	**100**

[a] mean particle size 19.27 μm (volume mean diameter)

The implants were prepared by the method of Example 1.

Example 3

Pharmacokinetic profiling

The implants of Examples 1 and 2 were implanted into 16 cows at a dose of 500μg/kg. The blood plasma concentrations of doramectin following implantation were measured, and the results are shown in Figure 1. It can be seen that in each case single-host tick activity was obtained for more than 50 days, and control of helminths was obtained for about 90 days.

Claims:

1. A solid subcutaneous implant consisting essentially of: at least one parasiticidal compound having low aqueous solubility; and conventional tabletting excipients including a bulking agent.

2. An implant as claimed in claim 1, wherein the parasiticidal compound has an aqueous solubility below 100 μg/ml.

3. An implant as claimed in claim 2, wherein the parasiticidal compound is an avermectin or a milbemycin.

4. An implant as claimed in claim 3, wherein the parasiticidal compound is doramectin.

5. An implant as claimed in any one of the preceding claims, wherein the bulking agent is lactose.

6. An implant as claimed in any one of the preceding claims, wherein the tabletting excipients include magnesium stearate.

7. An implant as claimed in any one of the preceding claims, wherein the tabletting excipients include a tablet disintegrant.

8. An implant as claimed in claim 7, wherein the tablet disintegrant is sodium starch glycolate.

9. An implant as claimed in any one of the preceding claims, wherein the parasiticidal compound makes up between 10 and 50% of the implant, by weight.

10. An implant as claimed in any one of the preceding claims, which is adapted for implantation into the ears of cattle or sheep.

11. An implant as claimed in any one of the preceding claims, which is rod-shaped.

12. A method for the treatment or prevention of parasitic infections which comprises administering an implant as defined in any one of claims 1-11 to an animal in need of such treatment.

13. A solid subcutaneous implant comprising at least one parasiticidal compound having low aqueous solubility; and conventional tabletting excipients including a bulking agent.

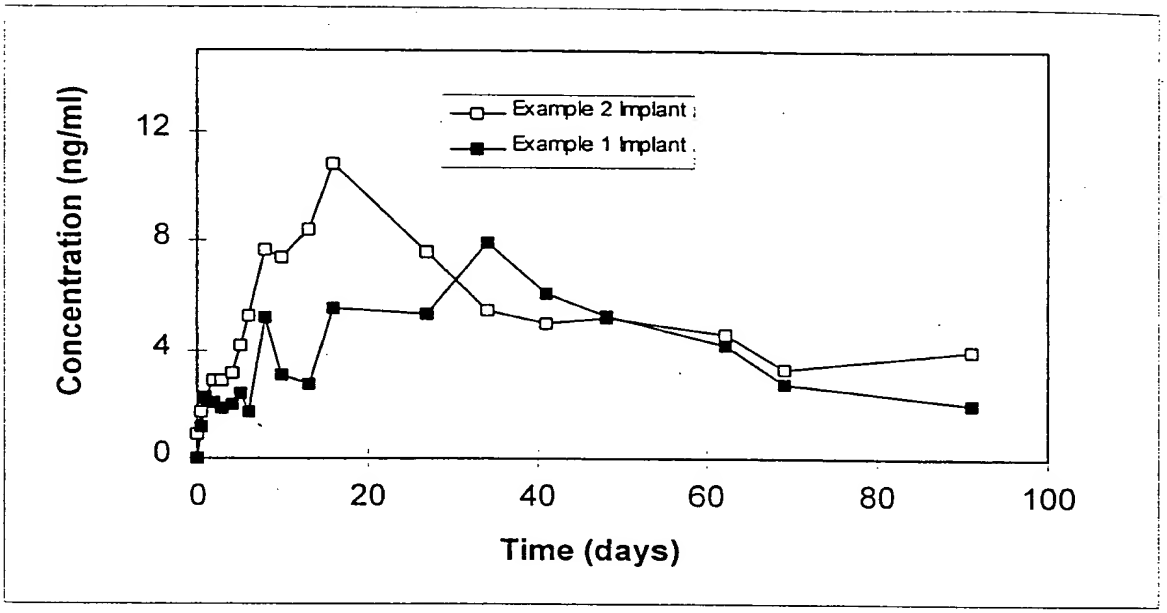

Example 2 Implant
Example 1 Implant
Concentration (ng/ml)
12
8
4
0
0
20
40
60
80
100
Time (days)

Figure 1